

Antagonists Argos Melanogasta	PGYRYLFAQSP-LTRLRQORKOPCKLFTVRKQREFLDEVNINSLSQCPK---CHRCPSHHTQSG-	Drosophila
	IEKLKEAKCKD-----YCHHNATCHVEVIFRED---RVSAVVPSCHPQGWETRCDRHYVQAF-	C. elegans
Agonists Lin-3 Vein Gurken Spitz Keren	DRSASGIPCN--FD--YGFHNGTGRMIPDIN-----EVY---GRQPTETFGNCKENKWPDSR-	D. Melanogasta
	ETEIQMLPQSEAYNTSFLNGGHCFOHPMVNN-----TVFHSGLGVNDYDGERCAKYSWNGD-	D. Melanogasta
	NITFPTYKCPETFDAWYCLNDAHFAVKIADL-----PVYS--GECALGFMCORCEYEKIDNT-	D. Melanogasta
	NVTFPIFACPTTYVAVYCLNDGTCTFTVKIHNE-----ILYN--GECALGFMCORCEYEKIDGS-	D. Melanogasta
	TGTSHLVKCAEKEKT-FGVNGGCFMVKDLIS-----NPSRYLCKQCPGFTGARGTENVPMKV-	Homo sapiens
NRG1_alpha NRG1_beta NRG2_alpha NRG2_beta NRG3 NRG4	TGTSHLVKCAEKEKT-FGVNGGCFMVKDLIS-----NPSRYLCKQCPNEFTGDRCONVVMASF-	Homo sapiens
	SWSGHARKCNETAKS-YGVNGGVYYIEGIN-----QLS---CKQPNGFFGQRCLEKLPRL-	Homo sapiens
	SWSGHARKCNETAKS-YGVNGGVYYIEGIN-----QLS---CKQPVGYTGDRQOQFAMVNF-	Homo sapiens
	ERSEHFKPCRDKDLA-YCLNDGECFVIETLTG-----SHK--HRCQKEGYQGVRRDQ-FLPKTD	Homo sapiens
	MPTDHEEPQGPSHKS-FCLNGGLCYVIPTIP-----SP---FCRCVENYTGARCEEVFLPGS-	Homo sapiens
EGF TGF_alpha Betacellulin Amphiregulin HB-EGF Epiregulin Epigen	SVRNSDSECPPLSHDG-YCLHDGVCMYTEALD-----KYA---GNCVVGYTGRCQYRDLKMW-	Homo sapiens
	AVVSHFNDCPDSHTQ-FCFH-GTGRFLVQED-----KPA---CVCHSGYVGARCEHADLLAV-	Homo sapiens
	KRKGHFSRCQPKQYKH-YCIK-GRGRFVVAEQ-----TPS---GVDEGYTGARCEVDFLYL-	Homo sapiens
	RNRKKNPQNAEFON-FOIH-GECKYIEHLE-----AVT---SKQOQEYFGARCEGSEKSMKTH-	Homo sapiens
	GLGKKRDPCLRYKD-FOIH-GECKYVKELR-----APS---GIDHPGYHGERCHGLSLPVE-	Homo sapiens
Conserved cysteine #:	VAQVSITKCSSDMNG-YCLH-GQCIYLVDMSE-----QNY---GRCEVGYTGARCEHFFLTVH-	Mus musculus
	VALKFSHPQLEDHNS-YCIN-GAQAFHHLK-----QAI---GRQFTGYTGARCEHLLTTSY-	

Figure 1

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Dros._melanogaster -----MPTTLMLLPMLLLLLLTAAAVAVGGTRLPLEVFEITPTTS--TADKHKSL
Dros._virilis      MASIRAHSLLLLLRLMLPLPLLLLLMLTGGAQSTRPLEVYELTPTASADSDAKHKSL
Musca_domestica    -----MLSLTIIFMLATHIINAGYSTRLPLEVYELTPNAAGGTDLKHKNL
                      :*. :*: . .*****;*: : : *
                      :

Dros._melanogaster QYTVVYDAK-----DISG-----AAAATG-----VASSTVKPATEQLTVVSISSTAAA
Dros._virilis      EY-AIYDPK-----ELTGAPKAAAAAAATT-----TTSSTARPSSEKPLAIAVVSISAE
Musca_domestica    EYSTINGSGSQHFLAINGRSKQHVSAAMEEPKMLSSHDSKAAATKTLTVSSMGTPSA
                      :* . : . : :* :* :* : : : : : : :

Dros._melanogaster EKDLAES-----RRHARQMLQKQQQ-----HRSIIGG---K
Dros._virilis      QQQQQQSELEPATQ-----AGRRARQMLQQQHR-----LSSSSSSSSNK
Musca_domestica    AATTTTSTSTATATATTNQLDRRRSRQMLDIMQKNHHDQTGNHKLPPVLSSGEGAATG
                      * :*: : : :* :

Dros._melanogaster HGD--RDVRILYQVGDSEEDLPVCAFNAVCSKIDLYETPWIERQCRCPESNRMPNNVIIH
Dros._virilis      HAHSVQDLRILYQVGDSEADLPVCAFNAVCSKIDLYETPWIERQCRCPESNRMPNNVIVH
Musca_domestica    ASHSQKDVRLYQVGNSEDDLPICAFNAVCSKIDLYETPWIERQCRCPAVNRSPEIITHH
                      .. :*:*****;* * :*:*****;***** * * : : *
                      <----->
                      A1 domain

Dros._melanogaster HHSHSSGSVDS--LKRYNYYEREKMMQHKR---MLLGEF---QDKKFESLHMKKLMQKLG
Dros._virilis      HHEHPHGTMSG-QKYRSYYEKEKLLQHKR---LLL-----DKKYESLHLKLMQKLG
Musca_domestica    HHKETASHSNHNSEKYHTFYEHSLAHQOQNKHLLDAASFVGDKKFDNLHLKLMHKLG
                      **... . * :*: : : : :* :* :* :*:*****;***

Dros._melanogaster AVYEDDL-----DHLDQS---PDYNDALP--YAEVQDNEFP-----RGSAHM
Dros._virilis      AVYEDDLQLPSAGDYVERS---PDYNEALPPAYEELADNELPQ-----APARSATHM
Musca_domestica    AVYEDDLNLPDYHRHEETNSALDDSEATLYADEIKDNEFFAHFAMKRQHLYSNTPHM
                      ***** . : : * * :* :* :* :* :* :* :* :*

Dros._melanogaster RHSGHRG-SKEPATTFIGGCPSSLGVEDGHTIADKTRHYKMCPVHKLFPVCTHFRDYTWT
Dros._virilis      RHSGHRG-LKE-AVSFIGGCPSNLGVEDGHTIADKTRHYKLCQPVHKLFPVCKHFRDYTWT
Musca_domestica    RHSGHTGGGHGKISYIGGCPSLGIEDGHTIADKTRHYKMCQPVHRLFPVCRHFRDYTWT
                      ***** * : :*:*****;*****;*****;*****;*****
                      <----->
                      A2 domain

Dros._melanogaster LTTAAELNVTEQIVHCRCPRNSVTYLTKEPIGNGSPGYRYLFCSPLTRLCQORKQPK
Dros._virilis      LTTAAELNVTEQVHCRCPKNSVTYLAKREPVPNSSTAYRYLFCSPLTRLCQORKQPK
Musca_domestica    LTTSPENMTTEQIVHCRCPRNSVTYLTKEPSEDGNGGYKYLFCSPLTRFCQORKQPK
                      ***;*: :*:*****;*****;***** :... :*:*****;*****
                      <----->
                      A2 (continued)
                      EGF domain

Dros._melanogaster LFTVRKRQEFLEVNINSLCCPKGHRCPSSHHTQSGVIAGESFLEDNIQTYSGYCMAND
Dros._virilis      LFTVRKRQEFLEVNINSLCCPKGHRCPSSHHTQSGVIAGESFLEDNIQTYSGYCMAND
Musca_domestica    LFTVRKRQEFIDEVNINALCCPKGHCPSHHTQSGVIAGETFLEDNIQTYSGYCMVND
                      *****;*****;*****;*****;*****;*****
                      <----->
                      EGF domain (continued)

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Figure 2

	Sequence ID #	
NRG1_alpha	1	TGTSHLVKCAEKEKTCVNGGECFMVKDLSNPSRYLCKCQPGFTGARCTENVPMKV
NRG1_beta	2	TGTSHLVKCAEKEKTCVNGGECFMVKDLSNPSRYLCKCPNEFTGDRQCQNYVMASF
NRG2_alpha	3	SWSGHARKCNETAKSYCVNGGVCYYIEGINQLS—CKCPNGFFGQRCLEKLPRL
NRG2_beta	4	SWSGHARKCNETAKSYCVNGGVCYYIEGINQLS—CKCPVGYTGDRCCQCFAMVNF
NRG3	5	ERSEHFKPCRDKDLAYCLNDGECFVIETLTGSHK-HCRCCKEGYQGVRCDDQFLPKTD
NRG4	6	MPTDHEEPCGSPSHKSFCLNGGLCYVIPTIP-SP-FCRCVENYTGARCEEVFLPGS
EGF	7	SVRNSDSECPLSHDGYCLHDGVCMYEALDKYA—CNCVVGYIGERCQYRDLKWW
TGF_alpha	8	AVVSHFNDCPDSTHTQCFH-GTCRFLVQEDKPA—CVCHSGYVGARCEHADLLAV
Betacellulin	9	KRKGFHSRCPKQYKHYCIK-GRCRFVAEQTPS—CVCDEGYIGARCERVDLFYL
Amphiregulin	10	RNRKKKNPCNAEFQNFCH-GECKYIEHLEAVT—CKCQQYFGERCGEKSMTKTH
HB-EGF	11	GLGKKRDPCLRKYKDFCIH-GECKYVVKELRAPs—CICHPGYHGERCHGSLPVE
Epiregulin	12	VAQVSITKSSDMNGYCLH-GQCIYLVDMSONY—CRCEVGYTGVRCEHFFLT VH
Epigen	13	VALKFSHPCLIEDHNSYCIN-GACAFHHELKQAI—CRCFTGYTGQRCEHLTLTSY
		* : * : * : * : * : * : * : * : * : * : * : * : * : * : *

Figure 3

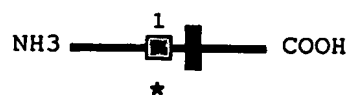
HUMAN	Sequence ID #	4/8	
		Exon A	Exon B
NRG1_alpha	14	TGTSHLVKCAFEKKTFCVNGGECFMVKDLSNPSRYLCKQCPQFTGARTENVPMKVO...	
NRG1_beta	15	TGTSHLVKCAFEKKTFCVNGGECFMVKDLSNPSRYLCKQCPNEFTGDRCONYVMASFY...	
Translated genomic locus	73, 128	TGTSHLVKCAFEKKTFCVNGGECFMVKDLSNPSRYLCK*	
NRG2_alpha	16	SWSGHARKQNETAKSYCVNGGVGYIEGINQLS---	CKQNGFFGQRCLEKLPRLYL...
NRG2_beta	17	SWSGHARKQNETAKSYCVNGGVGYIEGINQLS---	CKQPVGYTGDRQQQFAMVNFY...
Translated genomic locus	74, 129	SWSGHARKQNETAKSYCVNGGVGYIEGINQLS---	CK*
NRG3	18	ERSEHFKPRDKDLAYCLNDGECFVIETLTGSH-KHCR	CKQKEGYQGVRCDO-FLPKTD...
Translated genomic locus	75, 130	ERSEHFKPRDKDLAYCLNDGECFVIETLTGSH-KHCR*	
NRG4	19	MPTDHEPFGPSHKSFCLNGGLGYVIPTIPSPF---	GRQVENYTGARCEEVFLPGSS...
Translated genomic locus	76, 131	MPTDHEPFGPSHKSFCLNGGLGYVIPTIPSPF---	GR*
EGF	20	SVRNSDSECLPSHDGYCLHDGVCMYIEALDKYA---	QNCVVGYIGERCQYRDLKWWE...
Translated genomic locus	77, 132	SVRNSDSECLPSHDGYCLHDGVCMYIEALDKYA---	CK*
TGF_alpha	21	AVVSHFNDCCPDSHTQFCFH-GTCRELVQEDKPA---	CVCHSGYVGARCEHADLLAV...
Translated genomic locus	78, 133	AVVSHFNDCCPDSHTQFCFH-GTCRELVQEDKPA---	CV*
Betacellulin	22	KRKGFHSRCPKQYKHVCTK-GRCRFWAEQTPS---	CVQDEGYIGARSERVDLFYLR...
Translated genomic locus	79, 134	KRKGFHSRCPKQYKHVCTK-GRCRFWAEQTPS---	CV*

Figure 4

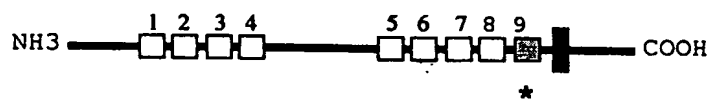
Amphiregulin Translated genomic locus	<p>...RNRKKKNPCNAEFQNE²³CIH-GECKYIEHLEAVT⁸⁰--CKCQOEYFGER¹³⁵CEKSMKTHS....</p> <p>...RNRKKKNPCNAEFQNE²³CIH-GECKYIEHLEAVT⁸⁰--CK*</p>
HB-EGF Translated genomic locus	<p>...GLGKKRDPCLRKYKDF²⁴CIH-GECKYVVKELRAPS⁸¹--CICHPGYHGER¹³⁶CHGLSLPVEN....</p> <p>...GLGKKRDPCLRKYKDF²⁴CIH-GECKYVVKELRAPS⁸¹--CM*</p>
Epiregulin Translated genomic locus	<p>...VAQVSITKCS²⁵SDMNGY⁸²CLH-GOCIYLVDMSONY¹³⁷--CRCEVGYTGVR¹³⁷CEHFFLTVHQ....</p> <p>...VAQVSITKCS²⁵SDMNGY⁸²CLH-GOCIYLVDMSONY¹³⁷--CR*</p>
Epigen(Mouse) Trans. mouse genomic locus Trans. human genomic locus	<p>...VALKFSHP²⁶CLEDHNSYCIN-GACAFHHEIKQAT⁸³--CRCFTGYTGOR¹³⁸CEHLLT¹³⁹TSYA....</p> <p>...VALKFSHP²⁶CLEDHNSYCIN-GACAFHHEIKQAT⁸³--CR*</p> <p>...IALKFSHL²⁶CLEDHNSYCIN-GACAFHHEIKAI⁸⁴--CR*</p>

Figure 4 (continued)

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i) TGF- α 

ii) Epidermal Growth Factor



iii) Notch 1

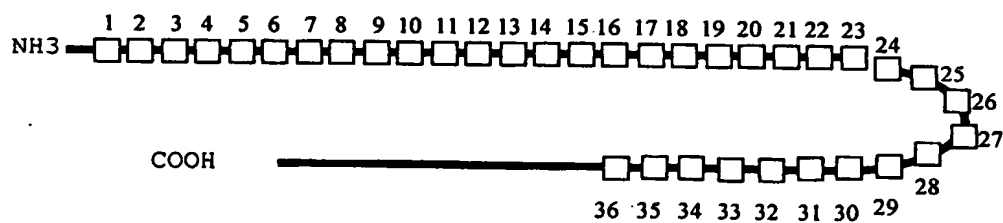


Figure 5A

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i) TGF alpha		Sequence ID #
EGF DOMAIN NUMBER		
1.	EGF_47_82 *	72
-----SEQUENCE-----		
QBSHTQVCF-HCT-GRFAVOEDKPAVCHSG--YVGAR--C		
ii) EPIDERMAL GROWTH FACTOR		Sequence ID #
EGF DOMAIN NUMBER		
1.	EGF_318_354	27
2.	EGF_360_395	28
3.	EGF_401_436	29
4.	EGF_439_476	30
5.	EGF_745_780	31
6.	EGF_835_868	32
7.	EGF_874_910	33
8.	EGF_916_951	34
9.	EGF_976_1012 *	35
-----SEQUENCE-----		
SKLR-KGNCST-SIVCGDIT--QSHLCMGATGYALSRDRKYG		
CALW-NHGG--TEGCKNLP--GSYACTCPVGFVWLPDGRKG		
EPRN-VSEC--SHDGVMTS--EGPICTGPDGSMTERDGRKG		
SSSPDNGCCS--QICVPLSP--VSWPCDPRGMDLDELKSG		
QLYQNGCCG--EHLCKGGL--GTAWGSCREGEMKASDGRKG		
QAPV--COS-MYARCTSPG--EDATCOGLKG--PAGDGRKG		
CEMG-VAVCPAPASCKGINTL--CGAVCRGSG--YQGDGPHG		
EOLG-VHSCGENAS-GITNLP--CGATCMCAGR--LSEPGHKG		
EPLSHDSXGL-HDGVCMATEALDKYACN--CVVG--YIGER--C		
iii) Notch1		Sequence ID #
EGF DOMAIN NUMBER		
1.	EGF_24_57	36
2.	EGF_63_98	37
3.	EGF_106_138	38
4.	EGF_144_175	39
5.	EGF_182_215	40
6.	EGF_222_254	41
7.	EGF_261_292	42
8.	EGF_299_332	43
9.	EGF_339_370	44
10.	EGF_376_409	45
11.	EGF_416_449	46
12.	EGF_456_487	47
13.	EGF_494_525	48
14.	EGF_532_563	49
15.	EGF_570_600	50
16.	EGF_607_638	51
17.	EGF_645_675	52
18.	EGF_682_713	53
19.	EGF_720_750	54
20.	EGF_757_788	55
21.	EGF_795_826	56
22.	EGF_833_867	57
23.	EGF_874_905	58
24.	EGF_912_943	59
25.	EGF_950_981	60
26.	EGF_988_1019	61
27.	EGF_1026_1057	62
28.	EGF_1064_1095	63
29.	EGF_1102_1143	64
30.	EGF_1150_1181	65
31.	EGF_1188_1219	66
32.	EGF_1226_1265	67
33.	EGF_1272_1305	68
34.	EGF_1312_1346	69
35.	EGF_1353_1384	70
36.	EGF_1392_1426	71
-----SEQUENCE-----		
CSQ-----PGETCLNGGKCEAANGTE-----ACVCG-GAFVGP		
GHS--TPCKNACTCH-VVDRRGVADYACSCA-EGESGPE		
GLT--NPCRNGGTCG-LTLETT--LYKCRCP-PGWSCKSC		
CAS--NPGANGGQC--TP-PPASYTQHCP-PSHGETG		
CGO--KPRLRHGGCTGHNEVGSY--FRCVER-ATHGGENC		
SSPSP--CONGGTRETGDV--THHCAGL-PGFTGQNC		
SPGNN--GNGGCAV-DGVN--TYNGPCP-PEWTGOYC		
CQL--MPNACONGCTCHNTHGGY--NGVCV-NGMTGEDC		
CAS--NAGEHCATCH-DRVA--SYNGECP-HGRGILLC		
GHS--NPGNEGSNOD-TNEV--NGKATCTCP-SGTGPAG		
EST--GANPCEHAGKCINTLGSE-----ECQCL-QGYTGPRC		
GVS--NPGCONDATCL-DOIG--EFGCMCM-PGYEGVHC		
CAS--SPGTHNGROL-DKIN--EFGCECP-TGFTGHLG		
CAS--TPCKNCAKEL-DGPN--TATGCVT-EGYTGTHC		
ODPDR--CHMC-SCK-DEVA--MTOLER-PGWTGHHG		
ESS--QPCRLRGTCQ-DFDN--AYLGROL-KGWTGPN		
CAS--SPG-DSCTCL-DKID--GYFGACE-PGWTGSMC		
CAG--NECHNGGTC--ED-GINGETCRCP-EGVHDPIC		
GNS--NPGVHCAGRD--SIN--GYKDCD-PEGWSGTNC		
GHS--NPGVNGGTCCK-D-MTS--GAVCTCR-EGESGPN		
CAS--NPGENKGTG--IDD--VAGYKONCL-PPATGATC		
CAR--SPERNCGECP-QSED-MES-FSCVGETAGARGQTC		
CVL--SPERHGASCO-NTHG--XYRGHCO-AGYSGRNC		
GRPNP-----CHNGGSCT-DGIN--TAFCDCL-PGFRGTFC		
CAS--DP--GRNGANCT-DCVD--SYTCTCP-AGFSGTHC		
CTESS-----CFNGGTCV-DGIN--SFTCLCP-PGFTGSYC		
GDS--RPFOLGGTCQ-DG--RGTHRCTCP-OGMTGENC		
GDS--SPCKNGGKCV-OT--HTOYRCECP-SGWIGHYG		
GPVAAQRQGVQVVARLCQHGLCV-DAGN--THHCRCQ-AGYTGSYC		
GSE--SPGQNGATCT-DYLG--GYSCKCV-AGYHGVNC		
GLS--HPCONGCTOL-DLPN--TYKCSOP-RGTGVHC		
ENPVDVRSRS--PKCFNNGTCV-DOVG--GYSCTCP-PGVGPRC		
GLS--NPGDARGTON-CVOR--VNDHCECR-AGHTGRR		
CKG--KPCCKNGGTCV-VASN-TARGHCKOP-AGFEGATC		
G--GSLRCLNGGTCISGPRSP--TGHL-CPFTGPFC		
CL--GGNPGYNGCTCEPTSESPE--YROLCP-AKENGHLC		

Figure 5B

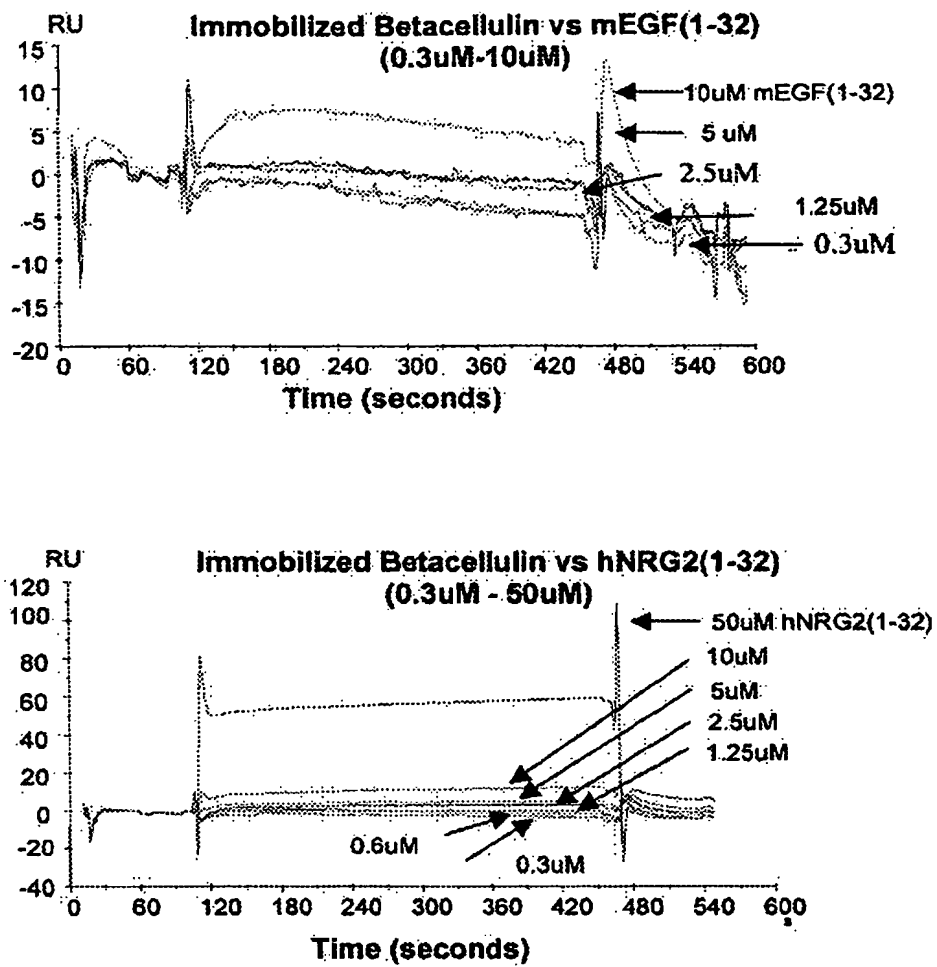


Figure 6